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cytokine production by primary cultures of human nasal and tracheal epithelial cells. *Respir Investig*. 2020;58(3):155–168.

8. Jackson DJ, Busse WW, Bacharier LB, et al. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2 [e-pub ahead of print]. *J Allergy Clin Immunol*. <https://doi.org/10.1016/j.jaci.2020.04.009>, accessed April 22, 2020.
9. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev*. 2020;19(6):102537.
10. Pellaia G, Vatrella A, Busceti MT, et al. Molecular and cellular mechanisms underlying the therapeutic effects of budesonide in asthma. *Pulm Pharmacol Ther*. 2016;40:15–21.
11. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;395(10223):473–475.
12. Liu F, Xu A, Zhang Y, et al. Patients of COVID-19 may benefit from sustained lopinavir-combined regimen and the increase of eosinophil may predict the outcome of COVID-19 progression. *Int J Infect Dis*. 2020;95:183–191.

Coronavirus disease 2019—associated urticaria with angioedema in a morbidly obese man successfully treated with glucocorticoids



The onset of severe urticaria has been linked to viral infections in both children and adults.¹ Here, we describe a patient who is a morbidly obese man, smoker, with severe refractory urticaria, angioedema, and systemic symptoms requiring oral glucocorticoids, and who was subsequently diagnosed as having coronavirus disease 2019 (COVID-19) and had a successful outcome. The patient was a 36-year-old obese man who presented with a complaint of acute urticaria (Fig 1). He woke up (day 0) with generalized erythema and pruritus with gradual onset of generalized urticaria (palms and soles included). He was seen in an emergency department (ED) and was prescribed methylprednisolone dose pack and an oral dose of diphenhydramine 50 mg twice daily. On day 6, he returned to the ED for a relapse of his symptoms and was continued on a dose of both oral prednisone 20 mg twice daily and oral diphenhydramine 50 mg twice daily; he was also started on a dose of oral cefdinir 500 mg 4 times daily. On day 9, he woke up with generalized erythema, pruritus, urticaria, and angioedema of his lips. When he arrived at the ED (within 20 minutes), he was experiencing dyspnea, cough, and wheezing. He was treated with nebulized albuterol, diphenhydramine, epinephrine, and famotidine, and was administered methylprednisolone intramuscularly and saline intravenously. He responded and was asymptomatic when discharged from the ED. He continued both oral prednisone 20 mg and oral diphenhydramine 50 mg, each twice daily, and stopped cefdinir.

He was seen in our clinic on day 11 and could not relate his urticaria to time, place, or action, but had experienced anosmia and ageusia the day before the visit. He had no other symptoms. His past medical, social, and family histories and review of systems were unremarkable except for a 15 pack-year smoking history (currently 2.5 packs/day). He had no history of asthma and worked as a door host at a bar.

Physical examination revealed an obese man (body mass index of 44) with normal vital signs and unremarkable examination findings other than slight erythema of the nasal mucosal membranes and scattered urticaria lesions on his torso. Complete blood cell count, serum tryptase, and COVID-19 tests were ordered. He was prescribed a dose of oral prednisone 20 mg twice daily and high dose of oral cetirizine. However, he continued oral diphenhydramine 50 mg twice daily instead. On day 13, his COVID-19 test result was reported to be positive. Complete blood cell count was within normal limits except for a white blood cell count of 13,100 cells/ μ L (reference range, 3.8–10.8 cells/ μ L) and absolute neutrophil count of 9419 cells/ μ L (reference range, 1500–7800 cells/ μ L), which was attributed to glucocorticoids. Serum tryptase level was 5.9 μ g/L (reference range, <11 μ g/L).

On day 16, his urticaria was controlled, and he had no other COVID-19 symptoms except for continued anosmia and ageusia. On day 18, he attempted to taper his dose of oral prednisone 20 mg to a single daily dose, and his urticaria had exacerbated. His smell and taste had returned. Both prednisone 20 mg and diphenhydramine 50 mg twice daily were continued. On day 22, he was asymptomatic, thus he began to taper his prednisone, started a dose of oral cetirizine 10 mg twice daily, and stopped diphenhydramine. His repeat COVID-19 test result was negative (day 20). He stopped all medications on day 27 and remained asymptomatic.

This patient had persistent refractory urticaria necessitating oral glucocorticoids for several weeks. He had no other clinical symptoms except for a mild systemic allergic reaction 9 days after the onset of urticaria. Such systemic symptoms have been reported in cases of severe urticaria.² He was morbidly obese and a heavy smoker, placing him at higher risk for severe COVID-19.³ He was immediately and continually treated with oral glucocorticoids. We speculate that a cause-and-effect relationship may have existed, such that COVID-19 caused his severe urticaria and a systemic allergic reaction, including acute bronchospasm, which was the only time he ever experienced wheezing symptoms. Cutaneous manifestations of COVID-19 have been described in a cohort of 88 Italian patients, 20% of whom had cutaneous symptoms (3.4% had urticaria) but none as a presenting sign or symptom.⁴ There was also a report of urticaria with facial angioedema on day 11 of a mild case of COVID-19, which resolved within 24 hours with high-dose antihistamine treatment. Glucocorticoids were not required, and the urticaria was not accompanied by any systemic signs or symptoms.⁵

Could systemic glucocorticoids be beneficial if started early at the onset of COVID-19? The very few retrospective studies evaluating glucocorticoid use in COVID-19 found mixed results and was only reported in severe cases.⁶ The only prospective study, entitled Randomized Evaluation of COVID-19 Therapy, found that a dose of dexamethasone 6 mg daily used in patients hospitalized with COVID-19 was associated with decreased mortality among those on invasive mechanical ventilation or oxygen.⁷ There was no benefit in mild to moderate cases not requiring supplemental oxygen. There are no reports of glucocorticoids being used from the beginning of COVID-19 for outpatients. Specifically, only dexamethasone and intravenous methylprednisolone have been used and only in hospitalized patients.⁵

Other than this case report, what could be the rationale for performing a controlled study evaluating the value of oral corticosteroids initiated as soon as COVID-19 was diagnosed? Triggers for asthma exacerbations include viral respiratory tract infections, and rhinovirus and respiratory syncytial virus are the most frequent viral triggers.⁸ The treatment of choice for these asthma exacerbations include prednisone or its equivalent. This patient

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Figure 1. Urticaria present on the patient's left shoulder.

was treated with a dose of 40 mg/day of prednisone from what seems to be the onset of his COVID-19. It appears to be an oxymoron that for severe, viral-induced, life-threatening asthma, glucocorticoids are the treatment of choice. In fact, other strains of coronaviruses can trigger an asthma flare. This case suggests a rationale for a controlled study using similar moderate doses of oral

glucocorticoids, initiated as close to COVID-19 onset as possible, with a goal of mitigating disease progression and hospitalization.

Thus, we suggest that COVID-19 could have caused this patient's severe urticaria, angioedema, and an associated systemic allergic reaction. In addition, glucocorticoids, in doses for treating acute asthma flares, could be beneficial in treating COVID-19.

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References

1. Imbalzano E, Casciaro M, Quartuccio S, et al. Association between urticaria and virus infections: a systematic review. *Allergy Asthma Proc.* 2016;37(1):18–22.
2. Doong JC, Chichester K, Oliver ET, Schwartz LB, Saini SS. Chronic idiopathic urticaria: systemic complaints and their relationship with disease and immune measures. *J Allergy Clin Immunol Pract.* 2017;5(5):1314–1318.
3. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19 [e-pub ahead of print]. *N Engl J Med.* <https://doi.org/10.1056/NEJMcp2009575>, accessed July 5, 2020.
4. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol.* 2020;34(5):e212–e213.
5. Adelino R, Andres-Cordon JF, Aracelis De La Cruz Martinez C. Acute urticaria with angioedema in the setting of coronavirus disease 2019. *J Allergy Clin Immunol Pract.* 2020;8(7):2386–2387.
6. Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: a systemic review and a clinician's perspective [e-pub ahead of print]. *Diabetes Metab Syndr.* <https://doi.org/10.1016/j.dsx.2020.06.054>, accessed July 5, 2020.
7. Horby P, Lim WS, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. 2020. Available at: <https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1>. Accessed July 4, 2020.
8. Castillo JR, Peters SP, Busse WW. Asthma exacerbations: pathogenesis, prevention, and treatment. *J Allergy Clin Immunol Pract.* 2017;5(4):918–927.